REMARKS

Claim Status

There are 49 claims pending, namely claims 1-49, among which claims 16-39, 42 and 43 have been withdrawn by the Examiner as being drawn to non-elected species and inventions. Claims 1-15, 40, 41 and 44-49 are being examined.

Claim Interpretation

a). The term "fluorophore compound"

In this Final Office Action, the Examiner responds to Applicant's previous claim interpretation that the term "fluorophore compound" is a unimolecular entity in light of the specification by stating that there is no definition of the term in the specification. More particularly, the Examiner contends that there is no statement in the specification of the following form: "The term "fluorophore compound" means...", "The term "fluorophore compound" is..." or "The term "fluorophore compound" refers to...", and thus the interpretation of the term as a unimolecular or multimolecular entity is the broadest reasonable interpretation in view of lack of its definition. Applicant respectfully disagrees.

As pointed out previously and reiterated herein, the instant specification clearly describes a fluorophore compound as a unimolecular entity. In particular, paragraph [0032] describes "the molecule containing the fluorophore and the quenching leaving group can be any type of molecule. For example, the molecule can be an organic compound, an organometallic compound, a nucleic acid, a peptide, a protein, a lipid, a carbohydrate, or other types of molecules." Also, Figures 2 and 3 of the instant specification provides examples of the fluorophore compound, which clearly demonstrate the relative locations of

the fluorophore group and the fluorescence quenching leaving group on the same molecule as one entity.

Applicant contends that the above description and drawings from the instant specification define the term "fluorophore compound" through the term usage in the context of the specification. The Court of Appeals for the Federal Circuit has ruled that the specification is the single best guide to the meaning of a disputed term and that even when guidance is not provided in explicit definitional format, the specification may define claim terms by implication such that the meaning may be found in or ascertained by a reading of the patent documents. See *Phillips v. AWH Corp.*, 415 F.3d 1303, 75 USPQ2d 1321 (Fed. Cir. 2005) (*en banc*); *Vitronics Corp. v. Conceptronic Inc.*, 90 F.3d 1576, 39 USPQ2d 1573, 1577 (Fed. Cir. 1996); and *Novartis Pharms. Corp. v. Abbott Labs.*, 375 F.3d 1328, 1334-35 (Fed. Cir. 2004) (copies enclosed herein for the Examiner's reference.)

b)-c). The term "fluorescence quenching leaving group"

The Examiner also states that the terms "leaving group" and "quenching" are described in the specification in terms of their functions and that there are no definitions in the specification, and as such, any fluorescent molecule is a fluorescence quenching leaving group.

In response, Applicant again submits that the instant specification clearly sets the metes and bounds of this term and that not all fluorescence quenching groups are considered as fluorescence quenching leaving groups according to the context of the present application.

In particular, the instant specification provides the following definition to the term "leaving groups" in paragraph [0035]:

> Leaving groups as in general are defined by (a) their ability to activate an atom (to which they are attached) for attack by a nucleophile group and (b) to leave (either simultaneously or subsequently) when the nucleophile does attack.

As to the term "quenching", the instant specification describes that nucleophilic attack on the quenched DNA causes release of the quencher group, which results in a ligated molecule that is now fluorescent due to the absence of the quencher group (*see*, paragraph [0019]), and that upon ligation with another molecule in intermolecular fashion, or with itself in intramolecular fashion, the quenching leaving group is displaced and the fluorophore is no longer quenched (*see*, paragraph [0031]). In addition, examples are given regarding quenched fluorescence. Example 2 of the instant specification describes that when beads containing a 7mer MUT probe autoligate a 13mer quenched electrophile probe to themselves, in the presence of the correct target DNA, the beads would become fluorescent, as the dabsylate group was lost and the nearby fluorescein label lost quenching. Such description and example indicate that quenched fluorescence in the context of the present invention involves a quenched electrophile probe, which is a unimolecular entity with both a fluorophore group (e.g., fluorescein) and a fluorescence quenching leaving group (e.g., dabsylate group) located close to each other thereon.

In addition, the leaving group itself is also a quencher in the context of the present application, such that when the bond is broken and the leaving group leaves, the fluorescence of the remaining molecule increases.

Furthermore, the instant specification provides multiple examples of fluorescence quencher (*see*, paragraphs [0041] and [0042].)

Applicant contends that the above description and examples from the instant specification define the term "fluorescence quenching leaving group" through the term usage

in the context of the specification. As implicated, the fluorescence quenching leaving group in the context of the present invention is not any fluorescence quenching group; rather, it is a group that is both a quencher and a leaving group. As pointed out above, the court has ruled that the specification may define claim terms by implication.

Additional Comments

On page 6 of the present Final Office Action, the Examiner appears to be simply repeating the section titled "Claim Interpretation" from the previous Office Action dated April 18, 2006. The terms "about 2 fold", "about 100 fold" and "about 1000 fold", however, are no longer recited in the currently pending claims. As such, paragraph No. 8 of the present Final Office Action is moot.

Claim Rejection – 35 USC §102

Claims 1-7, 9 and 11-15 remain rejected under 35 USC §102(a) as allegedly being anticipated by Sando et al. (J. Am. Chem. Soc., vol. 124, pp. 2096-2097, February 2002, "Sando"). Applicant respectfully traverses this rejection.

As pointed out previously and reiterated herein, Sando describes the inventor's own work on which the instant invention was based. In addition, Sando was published within the year before the effective filing date of the present application. In order to overcome this rejection, Applicant herewith submits a declaration under 37 C.F.R. §1.132 showing that the work described in Sando is not by "another".

In light of the declaration, Applicant respectfully requests that the novelty rejection over Sando be withdrawn.

Claims 1-8, 10, 11 and 14 are rejected under 35 USC §102(a) as allegedly being anticipated by Livak et al. (PCR Meth. Appl., vol. 14, pp. 357-362, 1995, "Livak"). Applicant respectfully traverses this rejection.

As presented previously and reiterated herein, Livak teaches a quenched probe of an oligonucleotide with fluorescent dyes at opposite ends. In particular, the fluorescent dyes are a fluorescein reporter dye (e.g. 6-carboxyfluorescein (6-FAM) phosphoramidite) and a rhodamine quencher dye (e.g. 6-carboxytetramethylrhodamine succinimidyl ester (TAMRA NHS ester)). Livak does not teach a fluorescence quenching leaving group, let alone a fluorophore compound comprising a fluorophore group and a fluorescence quenching leaving group, as claimed in the present application.

In detail, the rhodamine quencher dye taught by Livak is not a leaving group. It is clear from Figure 1 on page 358 that the quencher dye of Livak does not leave the oligonucleotide probe; rather, the fluorescein reporter dye leaves the probe when cleavage occurs between the fluorescein and rhodamine dyes. When the cleavage occurs, the fluorescence intensity of the fluorescein dye increases because the fluorescein is no longer quenched. Also see the middle column, page 357 of Livak.

In the present Final Office Action, the Examiner has not provided any reasoning as to how the structure of Livak's probe is such that the quencher would leave the probe under nucleophilic attack. In fact, the Examiner's above notion is not supported by Livak's teaching at all, especially *see* Figure 1, which demonstrates that the quencher dye (labeled as "Q") remains on the probe even after the cleavage. On the other hand, the fluorescein reporter dye (labeled as "R") leaves the probe after the cleavage.

In view of the above remarks, Applicant again submits that the oligonucleotide probe taught by Livak is not the same as the fluorophore compound of the present application. As such, the present novelty rejection over Livak should be withdrawn.

Claims 1, 5-7, 9 and 12-14 are rejected under 35 USC §102(a) as allegedly being anticipated by Xu et al. (Nat. Biotechnol., vol. 19, pp. 148-152, February 2001, "Xu"). Applicant respectfully traverses this rejection.

As presented previously and reiterated herein, Xu teaches two 7-mer probes (mutant and wild type) constructed with 3'-end phosphorothioate groups to act as nucleophiles in the ligation reaction and labeled with either the rhodamine (ROX) (for the mutant probe) or hexachlorofluorescein (HEX) (for the wild type probe), as well as one 13-mer probe (universal probe) internally labeled with 5-carboxyfluorescein (FAM). *See*, Sections titled "Design of autoligation probes" on page 148 and titled "Energy transfer probe design" on page 150. Xu further teaches that FAM is the donor dye of fluorescence resonance energy transfer (FRET) and ROX or HEX is the acceptor dye of FRET. However, Xu does not teach or suggest a fluorescence quenching leaving group for their 13-mer or 7-mer probe, let alone a fluorophore compound comprising a fluorophore group and a fluorescence quenching leaving group, as claimed in the present application.

In detail, FAM comprised in Xu's 13-mer probe is a fluorophore group that is considered to be the donor dye of FRET. Xu is completely silent on any fluorescence quenching leaving group as part of their 13-mer probe. In fact, it is clear from Figure 3 that Xu's 13-mer probe does not comprise a fluorescence quenching leaving group. Whereas, ROX or HEX comprised in their 7-mer probe, considered as the acceptor dye of FRET, is a fluorescence quencher but not a leaving group. *See*, Figure 3 of Xu.

In the present Final Office Action, the Examiner states that both ROX and HEX do quench the fluorescence of the donor dye as they are acceptor dyes. However, the difference between Xu and the present invention is not whether ROX or HEX quenches the fluorescence of the donor dye; rather, it is whether the quencher is also a leaving group. It is clear from the teachings of Xu that neither ROX nor HEX is a leaving group.

Furthermore, as discussed above under the Section titled "Claim Interpretation", the fluorophore compound of the present application is a unimolecular entity. That is, the fluorophore group and fluorescence quenching leaving group are comprised in the same molecule as one entity. It is clear that neither the 13-mer nor the 7-mer probe taught by Xu would be the same as the fluorophore compound of the present application for two reasons: 1) the fluorescein (i.e., FAM) and the fluorescence quencher (i.e., ROX or HEX) taught by Xu are not comprised in the same probe as one entity; and 2) the fluorescence quencher ROX or HEX is not also a leaving group.

In view of the above remarks, Applicant again submits that the 13-mer and 7-mer probes taught by Xu are not the same as the fluorophore compound of the present application. As such, the present novelty rejection over Xu should be withdrawn.

Claim Rejection – 35 USC §103

Claims 40, 41, 44, 46 and 47 are rejected under 35 USC §103(a) as allegedly being unpatentable over Sando, Tyagi et al. (U.S. Pat. No. 5,925,917, "Tyagi") and Stratagene Catalog (page 39, 1988, "Stratagene"). Applicant respectfully traverses this rejection.

As discussed above, Sando is not a valid prior art reference.

As presented previously and reiterated herein, Tyagi teaches molecular beacons for allele discrimination (*see,* abstract.) In particular, molecular beacons are hairpin-shaped

oligonucleotide probes that report the presence of specific nucleic acids in homogenous solutions. When they bind to their targets, molecular beacons undergo a conformational reorganization that restores the fluorescence of an internally quenched fluorophore. The fluorophore becomes unquenched because the conformational reorganization of the molecular beacons (i.e., opening up of the hairpin) leads to the separation of the fluorophore from the quencher. *See*, Figure 1 of Tyagi. That is, the quencher does not leave the molecular beacons, and physically it remains part of the same molecule as the molecular beacons. As such, the quencher taught by Tyagi is not the same as the fluorescence quenching leaving group of the present application. In fact, Tyagi does not teach or suggest any leaving groups, let alone a first nucleic acid probe comprising a fluorophore group and a fluorescence quenching leaving group, as claimed in the present application. In addition, Tyagi is completely silent on a nucleophilic group-containing nucleic acid probe.

Stratagene discloses in general combining reagents into kit formats. Stratagene does not deal with fluorescent probes.

In view of the above remarks, Tyagi in view of Stratagene would not have motivated one of ordinary skill in the art to produce a kit comprising first and second nucleic acid probes, wherein the first probe comprises a fluorophore group and a fluorescence quenching leaving group and the second probe comprises a nucleophilic group, as claimed in the present application. Rather, the combined teaching of Tyagi and Stratagene would, at most, lead to production of a kit comprising molecular beacons, which would be a different kit from that of the present application. As such, the present obviousness rejection should be withdrawn.

Claims 48 and 49 are rejected under 35 USC §103(a) as allegedly being unpatentable over Sando, Tyagi and Stratagene as applied to claim 40 above, and further in view of Seitz

et al. (Angew. Chem. Int. Ed., vol. 39, pp. 3249-3252, 2000, "Seitz"). Applicant respectfully traverses this rejection.

As discussed above, Sando is not a valid prior art reference. Tyagi and Stratagene, along or combined, do not teach or suggest a kit comprising first and second nucleic acid probes, wherein the first probe comprises a fluorophore group and a fluorescence quenching leaving group and the second probe comprises a nucleophilic group, as claimed in instant claim 40.

As presented previously and reiterated herein, Seitz teaches a doubly labeled peptide nucleic acid (PNA) probe having appropriately appended fluorescence donor and fluorescence quencher groups located close in proximity. *See*, Figure 1 of Seitz. When the probe sequence anneals to the target sequence, a structural reorganization increases the donor-quencher distance within the duplexes and fluorescence occurs. That is, the quencher does not leave the PNA probe of Seitz. Such PNA probe has a structural analogy to the molecular beacons of Tyagi. It is clear that Seitz does not cure the deficiencies of Tyagi and Stratagene. Even if one skilled in the art were motivated to combine the teachings of Tyagi, Stratagene and Seitz, he or she would not have produced a kit comprising first and second peptide nucleic acid (PNA) probes, wherein the first probe comprises a fluorophore group and a fluorescence quenching leaving group and the second probe comprises a nucleophilic group, as claimed in the present application (*see*, instant claims 40, 48 and 49). Rather, the combined teachings of Tyagi, Stratagene and Seitz would, at most, lead to production of a kit comprising the molecular beacons of Tyagi or the PNA probes of Seitz, which kit would be different from that of the present application. As such, the present obviousness rejection should be withdrawn.

Rejoining of Non-elected Groups and Species

Applicant respectfully requests that the method claims of Groups II and III be rejoined with the product claims of Group I that are currently under the examination if the Examiner finds the product claims are allowable upon considering the present remarks. *See*, MPEP §821.04.

Also, Applicant respectfully requests that the claims directed to the non-elected species be rejoined with the claims directed to the elected species for further examination if the Examiner finds the claims directed to the elected species are allowable upon considering the present remarks. *See*, MPEP 809.02(a).

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This response is filed timely and no fee is believed to be due. However, should any fees be required for any reasons relating to this document, the Commissioner is authorized to deduct said fee from Howrey LLP Deposit Account No. 08-3038/12665.0024.NPUS01.

Respectfully submitted,

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